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The emerging questionable benefit of sorafenib as a neo-adjuvant in HCC patients treated with Y-90 radioembolization pending liver transplantation

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The constantly enlarging waiting lists for patients with hepatocellular carcinoma (HCC) referred for liver transplantation (LT) has been a driving force for development of improved loco-regional as well as systemic treatment modalities. Tumour progression after enlisting of patients for LT using the Milan criteria may vary between 10% and 23% and more, while delisting is a relatively frequent consequence [1]. Furthermore, a large number of patients present with tumour burden beyond the even extended Milan criteria. Tumour down-staging of such patients pending resection or as a bridge to LT has been repeatedly suggested using transarterial chemoembolization (TACE), radiofrequency ablation (RF), radioembolization (RE), external beam irradiation, and even systemic treatment with sorafenib [2–5]. At present, information regarding the relative efficacy, tolerability, and safety of one loco-regional modality over the other or *vs.* the standard of care treatment with sorafenib in defined BCLC stages is mainly derived from retrospective and/or non-randomized clinical trials (for example [6–8]). Indeed, comparative prospective, randomized phase III clinical trials of the available treatment options for HCC are extremely difficult to conduct due to the heterogeneous biologic properties of tumours and hosts, the impact of intervention such as LT, as well as the requirement for a long follow-up and a very large study population [9,10].

In this context, treatment with Yttrium-90 (^{90}Y) radio-embolization (RE) using either resin or glass microsphere injection into the hepatic artery, has been at the focus of attention among hepatologists, oncologists, and invasive radiologists for more than a decade [11–13]. It has been evaluated in phase I and phase II clinical trials for patients with advanced hepatocellular carcinoma (HCC) demonstrating acceptable safety as well as promising efficacy and has been suggested as a mean for down-staging HCC pending liver transplantation in patients with intermediate and advanced disease including those with portal vein invasion. Exposure to the beta emission released by Yttrium 90 radiation (t/2 2.67 days), leads to endothelial, tumour, and stromal cell injury and cell death. However, to quote from the 2012 EASL guidelines on treatment of HCC: "Cohort studies reporting long-term outcomes showed a median survival time of 17.2 months for patients at intermediate stages and 12 months for patients at advanced stages and portal vein invasion. Objective response rates range from 35% to 50%. Around 20% of patients present liver-related toxicity and 3% treatment-related death. Despite the amount of data reported, there are no randomized controlled trials (RCT) testing the efficacy of ^{90}Y radioembolization compared with chemoembolization or sorafenib in patients at intermediate or advanced stage, respectively. Further research trials are needed to establish a competitive efficacy role in these populations" [14]. The lack of evidence obtained from phase III RCTs using RE mentioned in the 2012 EASL HCC guidelines is about to change and at least 6 RCTs comparing RE to transarterial chemoembolization (TACE) or sorafenib are in progress with estimated completion between 2014 and 2018 [12].

One rational for adding sorafenib to RE or TACE is based on the assumption that this neo-adjuvant will attenuate the flush of angiogenic factors (i.e., VEGF) released following arterial embolization and hypoxia.

In the present issue of the journal, Kulik and co-workers from the Northwestern University in Chicago, report the results of a first and small prospective randomized pilot study evaluating the safety and adverse events of ^{90}Y RE administered with or without Sorafenib in HCC patients awaiting liver transplantation [15]. This report complements a recent paper by the same group evaluating the radiological and pathological changes observed in the same group of patients receiving either monotherapy with RE or combined ^{90}Y and sorafenib treatment as a bridge to liver transplantation [16].

The study population consisted originally of 23 patients with confirmed HCC either through imaging criteria or histology. After exclusion of 3 patients, 20 candidate patients for liver transplantation (the majority with chronic hepatitis C) were prospectively randomized to receive either RE monotherapy (using TheraSphere, BTG, Canada) or sorafenib with ^{90}Y RE. In the combination group, sorafenib, 400 mg twice daily, was started ~14 days prior to RE and continued for up to 12 months and discontinued once the patient reached the number 1 position on the LT waiting list. The sorafenib dose was adjusted throughout the treatment period according to toxicity. The majority of patients had

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unilobar and unifocal tumours (n = 18). Median lesion diameter was 2.9 cm (range 1.7–5.6 cm) and 3.3 cm (1.1–4.5) for the ^{90}Y alone and the combined RE and sorafenib group respectively, most of them being classified as T2 UNOS stage. The baseline biological profile as determined by blood count, INR and creatinine levels was similar for both groups except for somewhat lower albumin and higher total bilirubin levels in the RE monotherapy group. Most patients underwent one session of RE except for 2 patients in the RE monotherapy group who received one and two additional RE treatments and one was also treated by TACE. In the combination group, three patients received one or more additional RE treatments as well as TACE or RFA. The small sample size of this study and relatively short follow-up period post transplantation (median follow-up 29.9 months) do not enable an assessment of comparative efficacy of the different pre-transplant treatment modalities. Yet, the data obtained prospectively in this pilot study, provide some preliminary information regarding the safety and tolerability of the treatment regimens and not less important, reiterate the difficulty in conducting prospective clinical trials in this difficult group of HCC patients.

Comments: The main results observed before LT include absolute grade 3–4 lymphotoxicity which was more pronounced in the RE monotherapy group. A rise in total bilirubin was equally distributed between both groups with a statistically non-significant trend of higher levels in the monotherapy group. Fatigue and abdominal pain were statistically more frequent in the monotherapy RE arm affecting 65% and 25% of patients respectively. Yet, the significance of these pre-transplant observations seems marginal and the true magnitude and biologic implications of these phenomena in this small group of patients remain to be determined. Seventeen patients underwent LT, one underwent liver resection and two died of HCC progression or sepsis prior to transplantation. Two patients in the monotherapy RE and one patients in the combined group died 49–970 days post LT. Survival rates were similar for both groups reaching ~70%.

Two important observations from this study require special attention: First, all 10 patients in the combined ^{90}Y RE and sorafenib group could not tolerate the initially prescribed dose of sorafenib. Consequently, sorafenib dosing was not optimal and only 3/10 patients received reduced doses of sorafenib until close to LT. Moreover, 50% of patients discontinued sorafenib altogether following side effects (described in detail in the report).

Second, biliary complications (mainly due to anastomotic strictures) and acute cellular rejection were observed within 30 days post LT, in 2/8 and 3/8 patients respectively, treated with the combination of sorafenib and RE prior to LT. In contrast, no such biliary complications or acute rejection were present in the RE monotherapy group.

These two observations raise the question whether the pre-transplant intolerance to sorafenib and the post-transplant biliary complications and rejection signify a safety signal regarding sorafenib therapy as a neo-adjuvant in patients receiving RE. Doubts regarding the usefulness of adding sorafenib to RE in patients not referred for LT, have already risen following a retrospective analysis of a small study in which 10 HCC patients with BCLC stage C were treated with sorafenib prior to RE [17]. In this study, overall survival of patients with advanced HCC receiving a combination of RE and sorafenib was lower compared to historical data in patients treated with RE or sorafenib alone. A recent, much larger retrospective, single center study compared the survival and safety of RE (n = 63 patients) with sorafenib (n = 74) [7]. Median overall survival of the two groups was similar reaching 14.4 months and 13.2 months in the sorafenib and RE group respectively. Median time to progression was significantly longer in the sorafenib group reaching 5 months compared to 3 months in the RE group. However, treatment was down dosed in 56/74 of patients (52 for sorafenib associated adverse events) while the RE patients tolerated treatment much better. Taking into account that sorafenib treatment did not augment the anti-tumoural effect of ^{90}Y as reported recently for the same cohort of patients [15]; the poor tolerability of sorafenib described in retrospective and as well as the current prospective studies; and the limitations of the discussed study as accurately described by the authors, it is very doubtful that sorafenib should be utilized as a neo-adjuvant for patients treated with RE. It is noteworthy that RE is gradually accepted as a valid loco-regional treatment modality worldwide despite the criticism regarding lack of objective evidence obtained through prospective phase III multicentre randomized trials comparing RE to other ablation modalities or sorafenib [10,14]. This study by Kulik *et al.* is indeed the first such prospective and randomized effort and this active group of investigators should be commended for this effort. However, the adverse events reported so far, the need in down dosing or discontinuation of sorafenib and the energy involved even in this very small study as well as the difficulties in recruitment and follow-up of HCC patients over a long period of time [9] cast doubt whether such an effort should be made to prove the additional and very doubtful benefit of sorafenib as a neo-adjuvant to RE.

Conflict of interest

The author declared that he does not have anything to disclose regarding funding or conflict of interest with respect to this manuscript.

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